

## REMARKS

Upon entry of these amendments, claims 1-20 will be pending in this application. Claim 1 has been amended herein to more precisely define the claimed invention. Specifically, claim 1 has been amended to specify that the “cartilaginous tissue comprises degenerating cartilage” and that the free glutamate is “liberated from said degenerating cartilage”. Support for these amendments can be found at least at page 5, lines 1-2 and 9 and at page 14, lines 12-14. Claim 10 has been amended herein to correct a typographical error. Claim 14 has been amended herein to recite the limitation “herniated intervertebral disc tissue” and to specify that the antagonist is administered spinally. Support for these amendments is found at least at page 2, line 17 and at page 14, lines 19-21. Claim 16 has been amended to correct an error in dependency. Claim 17 has been amended to incorporate all of the limitations of the claims from which it depends, (*i.e.*, claims 1 and 15). New claim 21 is supported by disclosure at page 2, lines 10-24, and page 14, lines 18-20, of the specification.

Accordingly, no new matter has been added herein.

### Objections to the Specification

The Examiner has objected to the specification at page 11, lines 13 for containing a typographical error. Applicant thanks the Examiner for pointing out this discrepancy. As requested by the Examiner, the word “trump” has been replaced by “pump” at page 11, line 13. As such, Applicant submits that this objection has been overcome and should be withdrawn.

### Claim Objections

The Examiner has objected to claim 10 because the spelling of the compound LAP-3 is incorrect. In response, Applicant has amended claim 10 to recite “L(+)-2-amino-3-phosphonopropionic acid (L-AP3)”. With this amendment, Applicant believes that this objection has been overcome. Moreover, Applicant has also made a similar amendment to the specification at page 6, lines 21-31.

The Examiner has also objected to claim 17 as being dependent upon rejected base claims. In response, claim 17 has been amended herein to incorporate all of the limitations of

claims 1 and 15. As acknowledged by the Examiner, Applicant submits that amended claim 17 should now be allowable.

**Claim Rejections--35 U.S.C. § 103**

Claims 1-13, 15, 16, and 19-20 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lawand, et al., Euro J of Pharmacology 324:169-77 (1997) ("Lawand et al.") in view of Stanfa, et al., Neuroscience 93(4):1391-98 (1999) ("Stanfa et al.") and further in view of Garrett, Biol. Res. For Nursing 1(4):310-20 ("Garrett"). According to the Examiner, "Lowland et al. [sic.] teaches the potential role of NMDA and non-NMDA receptors in nociception and attenuation of pain-related behaviors by application of NMDA and non-NMDA receptor antagonists after full development of knee joint inflammation ... Stanfa et al. teaches that GluR5 receptors due to their restricted location may represent a better analgesic target ... Garrett teaches the crucial role of excitatory amino acid, glutamate, NMDA and non-NMDA receptors in pain transmission, pain modulation, central sensitization and the sensation of hyperalgesia . . ." (Office Action at pages 3-4). Thus, the Examiner concludes that it would have been obvious to use NMDA and non-NMDA receptor antagonists in a method of treatment to alleviate pain. Applicant traverses.

Claim 1 has been amended herein to specify that the claimed method for alleviating pain in a mammal comprises contacting a neuronal cell of a cartilaginous tissue with a glutamate receptor antagonist, wherein the cartilaginous tissue comprises degenerating cartilage that liberates free glutamate and wherein the glutamate receptor antagonist inhibits binding of the free glutamate to the glutamate receptors on the neuronal cell, thereby alleviating pain. None of the cited references teaches or suggests such a method.

Specifically, Lawand et al. describes the role of excitatory amino acid receptor involvement in peripheral nociceptive transmission. Lawand et al. injected combinations of excitatory amino acids into the knee joints of rats in order to induce the development of hyperalgesia and allodynia. Subsequent intra-articular injection of NMDA or non-NMDA glutamate receptor antagonists was able to attenuate these symptoms of hyperalgesia and allodynia. (See, Lawand et al., Abstract). However, there is no teaching or suggestion in Lawand et al. of the use of a glutamate receptor antagonist to inhibit binding of free glutamate liberated from degenerating cartilage tissue to glutamate receptors in order to alleviate pain. Moreover, Lawand et al. observed that the administration of individual excitatory amino acids

failed to produce symptoms of heat hyperalgesia or mechanical allodynia. (See, Lawand et al. at page 174, 1<sup>st</sup> column).

The addition of Stanfa et al. (either alone or in combination with Garrett) does not cure these deficiencies in the teachings of Lawand et al., as neither Stanfa et al. nor Garrett describes or suggests a method for inhibiting free glutamate released from degenerating cartilage tissue from binding to glutamate receptors on a neuronal cell of a cartilaginous tissue. Rather, Stanfa et al. examined a non-NMDA receptor antagonist (NBQX) as well as a KA receptor antagonist (LY382884) in order to examine the role in non-NMDA receptors in the spinal transmission of nociception in normal animals as well as animals with carrageenan inflammation. Likewise, while Garrett reviews the role of metabotropic glutamate receptor 1A in pain transmission and in central sensitization and indicates that L-AP3 exhibited an antinociceptive effect in animals linking effective treatment of hyperalgesia with this receptor (see Garrett at page 316, 2<sup>nd</sup> column), Garrett does not describe or suggest the use of glutamate antagonists to block the binding of free glutamate released from degenerating cartilage.

Therefore, the combination of Lawand et al, Stanfa et al., and/or Garrett does not teach or suggest all of the limitations of the invention recited in claim 1, as amended herein. Because of this, the ordinarily skilled artisan would not have been motivated to combine the teachings of these references in order to develop the claimed methods of alleviating pain associated with degenerating cartilage. As such, Applicant submits that this claim is not obvious in view of these references. Thus, this rejection has been overcome and should be withdrawn.

Moreover, dependent claims 2-13, 15-16, and 19-20 each depend (directly or indirectly) from amended claim 1. As such, they necessarily contain all of the limitations of that claim. Therefore, for the reasons articulated above, Applicant submits that these dependent claims are also non-obvious in view of Lawand et al., Stanfa et al., and/or Garrett. Thus, this rejection of these claims should also be withdrawn.

Claim 18 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lawand et al., Stanfa et al., and Garrett, as applied to claims 1-13, 15-16, and 19-20, and further in view of Takahashi et al., Pain 75:391-94 (1998) ("Takahashi et al."). According to the

Examiner, “Takahashi teaches the epidural administration of NMDA receptor antagonist ketamine to relieve neuropathic pain”. (Office Action at page 4). Applicant traverses.

Claim 18 depends from amended claim 1. Thus, it necessarily contains all of the limitations of that claim. As discussed above, the combination of Lawand et al., Stanfa et al., and Garrett, does not teach or suggest all of the limitations of claim 1 (and, hence, of dependent claim 18), because these references fail to describe or suggest methods of alleviating pain by using glutamate receptor antagonists to inhibit the binding of free glutamate released from degenerating cartilage tissue to glutamate receptors on a neuronal cell in a cartilaginous tissue. The addition of Takahashi et al. does nothing to cure these deficiencies. Rather, Takahashi et al. is concerned with the use of ketamine (an NMDA-receptor antagonist) to alleviate neuropathic pain following injury to the nervous system. There is no discussion or suggestion in Takahashi et al. of inhibiting the binding of free glutamate released from degenerating cartilage tissue in order to alleviate pain.

Thus, Applicant submits that the combination of Lawand et al., Stanfa et al., Garrett, and Takahashi et al. does not teach or suggest all of the limitations of claim 18. As such, this claim is not obvious in view of these references (alone or in combination). Therefore, this rejection has been overcome and should be withdrawn.

Claim 14 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lawand et al., Stanfa et al., Garrett, and Takahashi et al., as applied to claims 1-13, 15-16, and 18-20, and further in view of Harrington et al., Spine 25(8):929-36 (2000) (“Harrington et al.”). According to the Examiner, “Harrington et al. teaches that disc radiculopathy can be treated with epidural glutamate receptor antagonists.” (Office Action at page 5). Applicant traverses.

Claim 14, which depends from amended claim 1, has been amended herein to specify that the glutamate receptor antagonist is administered spinally. As described above, the combination of Lawand et al., Stanfa et al., Garrett, and Takahashi et al. does not teach or suggest all of the limitations of amended claim 1 (and, therefore, of amended claim 14). The addition of Harrington et al. does not cure these deficiencies.

Specifically, there is no teaching or suggesting in Harrington et al. of the spinal administration of glutamate receptor antagonists to alleviate pain. Rather, Harrington et al. merely suggests that disc radiculopathy may be treated with epidural glutamate receptor administration antagonist (see Harrington et al., Abstract). Moreover, Harrington et al. also teaches that “it is not yet known whether free glutamate from disc material arriving at the DRG affects nociception. . . .” (Harrington et al. at p. 935, 1<sup>st</sup> column).

The combination of Lawand et al., Stanfa et al., Garrett, Takahashi et al., and/or Harrington et al. does not teach or suggest all of the limitations of claim 14, as amended herein. Moreover, based on the teachings of Harrison et al. (either when considered alone or in combination with Lawand et al., Stanfa et al., Garrett, and/or Takahashi et al.), Applicant submits that the ordinarily skilled artisan would not have had a reasonable expectation of success in alleviating the pain associated with a herniated disc via the spinal administration of a glutamate receptor antagonist. As such, Applicant submits that the addition of Harrington et al. to the combination of Lawand et al., Stanfa et al., Garrett, and/or Takahashi et al. is insufficient to establish a proper *prima facie* case of obviousness. Thus, this rejection should be withdrawn.

## CONCLUSION

Applicant submits that this paper is fully responsive and that the application is in condition for allowance. Such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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